

Study Title: Non-Randomized, Non-Blinded, One-Arm Study

**Evaluating the Performance and Safety of Surgical** 

**Navigation for Spinal Surgery.** 

Protocol Number: IGT-XCY607-130099

**Protocol Version:** Version 7.0

Protocol Date: 04 October 2016

**Protocol Title:** Observational Clinical Study with Surgical

Navigation to Plan, Position and Check Instrument

**Placement for Spine Surgery Interventions** 

**Analysis Type:** Final

**Analysis Plan Version: 1.0** 

Analysis Plan Date: 31 May 2018

**Author(s):** 

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# 1 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect	
AE	Adverse Event	
AK	Air Kerma	
BMI	Body Mass Index	
СВСТ	Cone Beam Computed Tomography	
CFR	Code Federal Regulations	
CI	Confidence Interval	
CRF	Case Report Form	
DAP	Dose Area Product	
DMC/DSMB	Data Monitoring Committee	
eCRF	Electronic Case Report Form	
FAS	Full Analysis Set	
IFU	Instructions for Use	

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IM	Intramuscular
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MEC	Medical Ethic Committee
MDD	Medical Device Directive
PP	Per-Protocol Analysis Set
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SN	Surgical Navigation System
SUS	System Usability Scale
USADE	Unanticipated Serious Adverse Device Effect

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#### 2 INTRODUCTION

This document details the final analyses for Study XCY607-130099, non-randomized, unblinded, one-arm study evaluating the performance and safety of Surgical Navigation System used for spinal surgeries. Related documents are the study protocol and electronic case report form (eCRF).

#### 3 STUDY OBJECTIVES

## 3.1 Primary Objectives

- To evaluate and estimate the proportion of success of pedicle screw placement using Surgical Navigation (SN) on post-procedural Cone Beam Computed Tomography (CBCT).
- To estimate the breach distance from the planned path.

## 3.2 Secondary Objectives

- To estimate the average procedure time.
- To estimate the average time (m:s) to insert a pedicle screw.
- To estimate the average length of hospitalization.
- To assess the clinical workflow related to easiness with System Usability Scale (SUS).
- To estimate the average total radiation dose exposed to the patients (Dose Area Product (DAP) and Air Kerma (AK)).
- To estimate the average total radiation dose exposed to the clinical operators.
- To describe where an adverse event (AE) leads to invasive intervention.
- To describe all AEs.
- To describe all Adverse Device Effects.
- To describe Device Deficiencies that could have let to Serious Adverse Events (SAEs).

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#### 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design

Study IGT-XCY607-130099 is non-randomized, unblinded, one-arm observational study.

## 4.2 Discussion of Study Design

Eligible patients admitted for spinal surgery involving screw placement with deformity correction (scoliosis/kyphosis), spinal fusion, degenerative disease requiring vertebral height correction, spondylolisthesis, stenosis (spinal of foraminal), fractures, to name a few are enrolled into study after being consented.

# 4.3 Selection of Study Population

Patients undergoing a spine surgery with pedicle screw placement.

#### 4.3.1 Inclusion Criteria

- Subject will be undergoing a spine surgery with pedicle screw placement
- Subject is 16 years of age or older
- Subject is able to give informed consent

#### 4.3.2 Exclusion Criteria

- Subject participates in a potentially confounding device or drug trial during the course of the study.
- Subject meets an exclusion criteria according to national law (e.g. pregnant woman, breast feeding woman)

#### 4.4 Treatments

#### 4.4.1 Treatment Groups

All patients enrolled are with intent to be treated with Surgical Navigation System

#### 4.4.2 Randomization

None.

#### 4.4.3 Study Duration

The study will continue until approximately 240 screws are implanted. It is estimated that the enrollment of 15 to 25 patients are necessary to collect sufficient data for the evaluation of the

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primary and secondary objectives of this clinical investigation to meet. It is expected that the study accrual period is approximately 7 months long.

#### 4.5 Site and or Stratum Enrollment Limits

Karolinska University Hospital

Neurosurgeon Department of Neurosurgery

SE-i 71 76 Stockholm

#### 4.6 Control to Minimize Bias

None was applied. This is an observational study.

#### 5 EFFICACY AND SAFETY VARIABLES

## 5.1 Efficacy Variables

Independent reviewers assessed the accuracy of screw placement according to the Gerztbein grading system for each placed screw. The determination of success of screw placement will be based on classification method by Gerztbein which was specifically modified for this study to include cervical screw placement in case of screw placement in this region. The assessment by three independent physicians will be considered primary for analyses of clinical performance endpoint.

Technical accuracy is based on distance measurements using the standard distance measurement capabilities in the system. This is performed by scientists from Philips.

Time recording is performed by study nurses on site and entered into the e-CRF.

The length of hospitalization is based on information from the hospital entered into the e-CRF. Dose is recorded by the system and by the Doseaware system.

#### **5.1.1** Primary Efficacy Variables

#### Clinical Performance

The primary endpoint for this study is the clinical performance of pedicle screw placement using Surgical Navigation defined in a binary endpoint of fail = 0 and success = 1. This is reported as the proportion of successful placement of the pedicle screw.

Initially, the screw placement will be assessed using the Gertzbein method with the following criteria: Grade 0 = breach of 0 mm, Grade 1 = lumbar and thoracic breach of < 2 mm, Grade 2 = lumbar and thoracic breach of > 4 mm. The 3 = lumbar

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assessments per pedicle is summarized by taking the median grade. Finally, Grades 0 or 1 will be categorized as a success of 1 otherwise a failure of 0 and proportion is reported.

No screw placement in the cervical region was needed to be performed.

#### Technical Performance

In addition to the clinical performance of SN, technical performance will be assessed as part of the primary endpoints, which is reflected in changes from the protocol (see Section 6.7).

The distance from the longitudinal axis of the screw and planned path (created by SN) are measured in mm from 3 different locations. (1) The head of the pedicle screw to the planned path, (2) the tip of the screw to the planned path, and (3) the distance of the longitudinal axis of the screw and the planned path at the smallest diameter of the pedicle (mm),

# 5.1.2 Secondary Efficacy Variables

- To estimate the average procedure time.
- To estimate the average time (m:s) to insert a pedicle screw.
- To estimate the average length of hospitalization.
- To assess the clinical work flow related to easiness with System Usability Scale (SUS).

## 5.2 Safety Variables

- To estimate the average total radiation dose exposed to the patients (Dose Area Product (DAP) and Air Kerma (AK)).
- To estimate the average total radiation dose exposed to the clinical operators.
- Adverse Events (AE)
- Surgical procedure-related complication
- Device Deficiencies that might have led to an SAE
- Adverse Device Effect (ADE)

#### **6 STATISTICAL METHODS**

#### 6.1 Sample Size

The planned sample size is approximately 240 screws. Assuming that the subjects will have 2 to 10 vertebrae's treated and the assumption that the majority of the patients will be scoliotic patients, approximately 15 to 25 patients will be needed to reach 240 screw placements.

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Based on data from prior studies, it is reasonable to assume that successful placement of screws with the Surgical Navigation System would be 85% with precision of approximately 10%. 240 screws or assuming that the subjects will have 2 to 10 vertebrae's treated and the assumption that the majority of the patients will be scoliotic patients, approximately 15 to 25 patients will be needed to reach 240 screw placements.

This would provide approximately 90% power to achieve a two-sided 95% confidence interval with at most a width equal to 10% of 85% successful placement of screws.

#### 6.2 General Consideration

The study is fully enrolled as originally planned and there is no impact on the power of the planned analyses.

#### **6.2.1** Analysis Population

#### 6.2.1.1 Full Analysis Set

Among 21 enrolled, 20 patients are included in this population. If an attempt is made with SN to perform surgical surgery on the patient, all data for the pedicles were included as the denominator. If multiple attempts or placements were performed, only the last event was recorded.

This resulted in 271 total pedicles in the analysis set.

Attempts made on pedicle where screws were not placed or screws placed without SN were categorized as a fail. Otherwise, fail/success was categorized according to the protocol following the modified Gertzbein's method

Kar-010 was excluded in the FAS, this will be listed as protocol deviation.

## 6.2.1.2 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set included only those screws that were placed among the 20 patients included in FAS. Those excluded were screws that were attempted but not placed, no image was available, (additional screws where SN was determined not used) and where hooks were placed. Which left with 253 possible pedicles.

Patients who meet any of the following criteria may be excluded from this analysis set:

- No screw was placed, although attempted.
- Hooks used instead of screws for surgery.
- Unforeseen circumstance in which the SN was not used i.e., There is not enough space between patient and detector to perform navigation, thickness of the patient (BMI of 37)

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prevented from being able to perform proper iso-centering of the spine for 3D imaging and to use SN, and screw was not attempted.

The specific classification of subjects to be excluded in the PP Analysis Set will be finalized prior to database lock. They will be listed in the Listing.

## 6.2.1.3 Safety Analysis Set

A Safety Analysis Set will include data from all 21 patients who were enrolled in this study, regardless of whether SN was attempted to be used or not.

This analysis set will be used in the analyses of safety variables as well as study device use.

## 6.2.2 Handling of Dropouts, Missing Data and Outliers

In general, values for missing data will not be imputed unless methods for handling missing data are specified.

No data are excluded due to being an outlier.

## 6.2.3 Data Handling Conventions and Transformations

- By-subject listings will be created for important variables in each eCRF module, and will be presented for all subjects enrolled and sorted by subject number, visit, and time (if applicable).
- Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. SD will be reported with one more decimal place than the other statistics aforementioned.
- Summary tables for categorical variables for baseline and safety data will include: N, n, and percentage. The tables for efficacy endpoints will include standard error, and 95% confidence intervals (CIs) on the percentage, where appropriate. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution. The denominator for the percentages will be the number of subjects in the Full Analysis Set at the same stratum or total as appropriate, unless otherwise specified. Missing data will be included as a row in tables where it is appropriate. All percentages will be presented as 1-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.
- Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

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## 6.2.4 Data Handling for Efficacy Endpoints

If there is a significant degree of non-normality for a continuous endpoint, analyses may be performed on log-transformed data or using nonparametric methods, as appropriate.

#### 6.2.5 Efficacy Subset

None.

# 6.3 Patient Disposition

#### **6.3.1** Subject Enrollment

A summary of subject enrollment will be provided. The denominator for this calculation will be the number of enrolled patients and number of screws. A listing of all enrolled patients will be generated to subject number, first treatment date, pedicle location, description of the exposure to device, and the reason for discontinuing device treatment and study.

In case of any screen failures, a by-subject listing for screening failures will be provided by screening identification in an ascending order with reasons for not being eligible for enrollment to the study.

# 6.3.2 Disposition of Subjects

Study device disposition will present the number of subjects who:

- were enrolled
- were enrolled but no screws used.
- SN used with screws.
- completed/discontinued treatment
- met primary study endpoint according to the investigator
- discontinued study device with summary of reason for discontinuation of the Study.

#### **6.3.3 Protocol Deviations**

The protocol deviations will be summarized by type of deviation in the clinical study report (CSR) based on all subjects enrolled. A listing will be provided for all important protocol deviations.

## 6.4 Demographics and Baseline Characteristics

Demographics including gender, age (years), weight (kg), height (cm), and body mass index (BMI, kg/m2) will be summarized for the Full Analysis Set. Gender will be summarized using

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summary statistics for categorical variables. Age (years), weight (kg), height (cm), and BMI (kg/m2) will be summarized using summary statistics for continuous variables. Age will be calculated as the number of years between date of birth and date of enrollment.

Age (years) = (date of enrollment - date of birth+1) / 365. 25 (round down to an integer)

BMI  $(kg/m^2)$  = weight /  $(height)^2$  (round to 1 decimal point)

A data listing will be presented for the above demographic data.

# 6.5 Study Compliance

Due to the nature of the investigational study device, compliance is not measured.

# 6.6 Medical History and Previous Interventions

Spinal disease history will be summarized using descriptive statistics and presented by treatment group based on the ITT Analysis Set.

Other baseline risk factors will also be summarized using descriptive statistics. No inferential statistics will be generated.

A by-subject listing of medical history will be provided.

## 6.7 Efficacy Analysis

Three physicians will be performed an independent review of the accuracy of pedicle screw placement based on classification method by Gerztbein which was specifically modified for this study. The assessment by three independent physicians will be considered primary for analyses of clinical performance endpoint. Technical accuracy is based on distance measurements using the standard distance measurement capabilities in the system. This is performed by scientists from Philips.

Time recording is performed by study nurses on site and entered into the e-CRF.

The length of hospitalization is based on information from the hospital entered into the e-CRF. Patient dose is recorded by the Philips Allura C-arm system and staff dose by Doseaware system.

#### 6.7.1 Primary Efficacy Definition and Analysis

No formal statistical hypothesis is planned and the primary endpoints will be presented as descriptive statistics only.

For both the clinical and technical performances, the analyses will be based on the PP Analysis Set.

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For the clinical performance, the proportion of successful screw placement are reported by overall, by Gertzbein Grade, by region-lumboscaral or thoracic and by location of the pedicles. In addition, the corresponding 95% CI as calculated using Exact Clopper-Pearson (ignoring the clustering by subject or location of the pedicles) and Cochran method described by Zhou [5] accounting for the patient level clustering of the pedicles will be presented.

For the technical performance, mean, median, SD, min and max of (1) The head of the pedicle screw to the planned path, (2) the tip of the screw to the planned path, and (3) the midsection of the screw to the planned path in mm will be presented. These statistics will be presented for overall, by region-lumbosacral or thoracic.

## 6.7.2 Secondary Efficacy Definition and Analysis

Secondary efficacy endpoints include:

- To estimate the average procedure time.
- To estimate the average time (m:s) to insert a pedicle screw.
- To estimate the average length of hospitalization.
- To assess the clinical work flow related to easiness with System Usability Scale (SUS).
- To estimate the average total radiation dose exposed to the patients (Dose Area Product (DA) and Air Kerma (AK)).
- To estimate the average total radiation dose exposed to the clinical operators.

#### **6.7.2.1** Average Procedure Time

Average Procedure Time is defined as average recorded time from incision to wound closure for each location in hours and minutes. Overall Average Procedure Time will be presented along with by Patient average. Median, SD, min and max procedure time.

In addition to the procedure time, the following 5 types of time measured will be reported with average, median, SD, and min and max in hours and minutes. (1) Total preparation time is defined as time admitted into the preoperative room till discharge from the room. (2) Preoperative Time before Table is defined as time from admitted in preoperative room to start time placed on the surgical table. (3) Preoperative Time on Table is defined as start time placed on surgical table to start of anesthesia administration. (4) Total time of Anesthesia Administration is defined as time from start to end of anesthesia administration. (5) Postoperative time after anesthesia is defined as time from end of anesthesia administration to end of admitting out of the preoperative room.

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## 6.7.2.2 Average Time to Insert Screw

Average Time to Insert Screw is defined as average recorded time from screw insertion to screw placement for each location and patient in minutes and seconds. Overall Average Time to Insert Screw will be presented along with by Patient average. Median, SD, min and max procedure time.

## 6.7.2.3 Average Length of Hospitalization

Average Length of Hospitalization is defined as average days from date of procedure until date of hospital discharge. Average Length of Hospitalization by Patient, Median, SD, min and max procedure time.

## 6.7.2.4 System Usability Scale (SUS) Questionnaire

Questionnaire is administered to 4 surgeons to assess the clinical workflow related to easiness to work in relationship to using the Surgical Navigation measured by the SUS scores. The raw scores on a scale of 0 to 4 are normalized to a scale of 0 to 100 in which the final score above 68 is considered to be above average and anything below to be below average. Individual score will be reported.

#### 6.7.2.5 Average Total Radiation Dose Exposure

#### Patient Dose

The total radiation dose is measured in Air Kerma (AK) (mGy) and dose area product (DAP) (Gy·cm²). Average dose per patient, median, SD, and min and max are reported for AK and DAP dose. Furthermore, for the DAP dose, the total procedural dose is broken into types of medical imaging (1) X-ray fluoroscopy, (2) Single Shot, and (3) XperCT and relative percentage to the total dose is reported at the individual patient level.

#### Occupational Dose

The cumulative radiation dose is measured by DoseWare in  $\mu$ Sv. Average dose per staff, median, SD, and min and max are reported for the radiation dose. In addition, the summary statistics are reported per each procedure/patient.

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## 6.7.3 Supplementary Efficacy Analysis

None planned

## 6.8 Safety Analysis

#### 6.8.1 Adverse Events

The focus of adverse event summarization will be on Device Deficiencies. All Adverse Events (AEs) occurring on study will be summarized on the Safety Analysis Set. All AEs will be listed in detail based on the Safety Analysis Set.

#### 6.8.1.1 Adverse Event Dictionary

AEs are not coded according to e.g. a Medical Dictionary for Regulatory Activities (MedDRA), however coded by trained professional and classified according to system organ system.

## 6.8.1.2 Relationship of Adverse Events to Surgical Procedure

The relationship of an AE to the component of study procedure should be assessed by the investigator using clinical judgment, describing the event as either unrelated, unlikely related, possibly related, probably related or causal relationship. Events for which the investigator did not record relationship will be considered related to the surgical procedure. Data listings will show relationship as missing.

#### 6.8.1.3 Serious Adverse Events

SAEs are those identified as serious in the clinical database.

#### **6.8.2** Device Deficiencies

Inadequacy of the investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

## 6.8.2.1 Adverse Device Effect (ADE) and Serious Adverse Device Effect (SADE)

The relationship of an AE to the component of study device should be assessed by the investigator using clinical judgment, describing the event as either unrelated, unlikely related, possibly related, probably related or casual relationship. Events for which the investigator did not record relationship will be considered related to study device. Data listings will show relationship as missing.

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## 6.8.2.2 Unanticipated Adverse Device Effect (UADE)

Events for which the investigator did not record relationship will be considered related to study device.

Data listings will show relationship as missing.

# 6.9 Subgroup Analysis

None planned.

#### 6.10 Strata and Covariates

Multiple screws will be used per patient over different possible spinal levels from the right or left side of the body. The spinal levels are T1, T2, T3,..., T12, L1, L2, L3, L4, L5, and S1. The number of screws will be stratified by patients and by spinal levels.

# 6.11 Multiple Comparison and Multiplicity

No formal statistical comparison will be performed and no adjustments are made for multiplicity.

#### 7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

## 7.1 Changes in the Conduct of the Study

Kar-010 will be excluded from the denominator and only included in the Safety Analysis although this patient was enrolled. Due to this patient's high (BMI of 37), the investigational device could not be utilized.

### 7.2 Changes in the Planned Analysis

The technical performance of measuring 1) distance from tip to planned path and 2) mid-line of screw to planned path, also the distance from head of screw to planned path with be analyzed, also as part of the primary objectives.

Kaplan-Meier estimates are not going to be used for the secondary efficacy analyses as outline in the protocol.

There are two changes in the way the data were collected. (1)To estimate the average time to insert a pedicle screw, the start time was not recorded from acquisition of the CBCT to the planned path from the Surgical Navigation as planned, but instead time had to be manually recorded with the start time of the actual screw placement. (2) For Patient Dose, only dose for the whole procedure was collected and not as originally planned to collect dose by preparation and acquisition of CBST for path planning, screw placement, preparation and acquisition of CBST for confirmation and planned path.

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To estimate radiation dose (Dose Area Product (DAP) and Air Kerma (AK)) delivered to patient for:

- Total procedure
- During preparation and acquisition of CBCT for path planning
- During screw/instrument placement (using fluoro).
- During preparation and acquisition of CBCT for confirmation
- Average procedure dose per planned path

#### 8 REFERENCES

Zhou, X; Obuchowski, N.A., and McClish, D.K. (2011). Statistical Methods in Diagnostic Medicine, 2<sup>nd</sup> edition, 110-111.

Gertzbein SD, Robbins SE. Accuracy of pedicular screw placement in vivo. Spine (Phila Pa 1976). 1990 Jan; 15(1): 11-14.

Bangor, A., Kortum, P.T. and Miller, J.A. (2008) An empirical evaluation of the System Usability Scale (SUS). International Journal of Human-Computer Interaction 24(6). 574-594.

#### 9 SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

#### 10 TABLES

Table Number	Title	Analysis Set
1.1.1	Subject Study Disposition (Device)	Enrolled
1.1.2	Subject Study Disposition (Device)	PP
1.2.1	Subject Study Device Disposition	Enrolled

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1.2.2	Subject Study Device Disposition	PP
1.3	Analysis Sets	Enrolled
1.4	Important Protocol Deviations	Enrolled
1.5.1	Subject Demographics and Baseline Characteristics	Enrolled
1.5.2	Subject Demographics and Baseline Characteristics	PP
2.1	Summary of Pedicle Surgery by Location and Patients	PP
Table Number	Title	Analysis Set
2.2	Frequency for Gertzbein Grade per Spinal Level	PP
2.3	Proportion of Successful Screw Placement by Anatomical Region	PP
3.1	Summary Statistics of Secondary Endpoint	PP
3.2	Summary of Total Surgical Procedure Time by Primary Reason of Procedure	PP
3.4	Summary of Length of Hospital Stay by Primary reason of procedure	PP
3.6	Summary of Patient Exposure Dose by Primary reason of procedure	PP/Safety
4.1	Overall Summary of Adverse Events	Safety
4.2	Overall Summary of Serious Adverse Events	Safety
4.1.1	Surgical Procedure-related Adverse Events	Safety
4.2.1	Surgical Procedure-related complication	Safety
4.3	Overall Summary of Device Deficiencies	Safety
4.3.1	Adverse Device Effect	Safety

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4.3.2	Serious Adverse Device Effect	Safety
4.3.3	Unanticipated Adverse Device Effect	Safety
4.4	Device Deficiencies might have led to a SAE	Safety

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# 11 FIGURES

Figure Number	Title	Analysis Set
1.1	Frequency of Gertzbein Grade by Spinal Level	PP
1.2	Boxplot of Breach Distance from Planned Path	PP
1.3	Boxplot of Screw Insertion Time	pp
	Boxplot for dose	pp

# 12 INDIVIDUAL SUBJECT DATA LISTINGS

Listing Number	Title	Analysis Set
1.1	Subject Disposition	Enrolled
1.3	Subjects and Pedicles Excluded From Any Analysis Set	Enrolled
1.4	Protocol Deviations	Enrolled
1.5	Subject Demographics and Baseline Characteristics	Enrolled and PP
2.1	Gertzbein Grade by Spinal Level	PP
2.2	Technical accuracy by Spinal Level	PP
3.1	Procedure Time by Patient and Spinal Level	PP
3.2	Insertion Time of Screw by Patient and Spinal Level	PP

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Listing Number	Title	Analysis Set
3.3	Length of Hospital Stay by Primary reason of procedure	Enrolled
3.4	Patient Dose	Safety
3.5	Occupational Dose	Safety
4.1	All Adverse Events	Safety
4.2	All Serious Adverse Events	Safety
4.3	Surgical Procedure leading to Adverse Events	Safety
4.4	All Device Deficiencies	Safety
4.5	All Adverse Device Effect	Safety
4.6	All Serious Adverse Device Effect	Safety
4.7	All Unanticipated Adverse Device Effect	Safety
4.6	Adverse Events Leading to Death	Safety
4.7	All Deaths	Safety

# **Document Revision History**

Version	Date	Author	Description of Change	Reason for Change
0.1	19 APR 2018		Initial Release	NA
1.0	31 MAY 2018		Initial Versionadded more information in Section 7.2	Initial Version

Document	<as applicable,="" per<="" th=""><th colspan="2" rowspan="3">Document title: Statistical Analysis Plan</th><th rowspan="2">Classification:</th><th rowspan="2">For internal use</th></as>	Document title: Statistical Analysis Plan		Classification:	For internal use
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# **Document Approval History**

Approved by	Role / Function	Signature & Date
	Project Statistician (SAP author)	
	Business Leader	
	Clinical Study Manager	
	Director of Biostatistics	

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